Pediatric Nephrology (2023) 38:593–604
https://doi.org/10.1007/s00467-022-05632-z

ORIGINAL ARTICLE

Cisplatin-induced nephrotoxicity in childhood cancer: comparison between two countries

Zulfan Zazuli[1,2] · Catharina J. P. Op 't Hoog[3] · Susanne J. H. Vijverberg[1] · Rosalinde Masereeuw[3] · Shahrad Rod Rassekh[4] · Mara Medeiros[5,6] · Rodolfo Rivas-Ruiz[7] · Anke H. Maitland-van der Zee[1] · Bruce C. Carleton[8,9,10]

Received: 4 January 2022 / Revised: 6 May 2022 / Accepted: 11 May 2022 / Published online: 24 June 2022

Abstract

Background Various definitions used to describe cisplatin nephrotoxicity potentially lead to differences in determination of risk factors. This study evaluated incidence of kidney injury according to commonly used and alternative definitions in two cohorts of children who received cisplatin.

Methods This retrospective cohort study included children from Vancouver, Canada (one center), and Mexico City, Mexico (two centers), treated with cisplatin for a variety of solid tumors. Serum creatinine–based definitions (KDIGO and Pediatric RIFLE (pRIFLE)), electrolyte abnormalities consisted of hypokalemia, hypophosphatemia and hypomagnesemia (based on NCI-CTCAE v5), and an alternative definition (Alt-AKI) were used to describe nephrotoxicity. Incidence with different definitions, definitional overlap, and inter-definition reliability was analyzed.

Results In total, 173 children (100 from Vancouver, 73 from Mexico) were included. In the combined cohort, Alt-AKI criteria detected more patients with cisplatin nephrotoxicity compared to pRIFLE and KDIGO criteria (82.7 vs. 63.6 vs. 44.5%, respectively). Nephrotoxicity and all electrolyte abnormalities were significantly more common in Vancouver cohort than in Mexico City cohort except when using KDIGO definition. The most common electrolyte abnormalities were hypomagnesemia (88.9%, Vancouver) and hypophosphatemia (24.2%, Mexico City). The KDIGO definition provided highest overlap of cases in Vancouver (100%), Mexico (98.6%), and the combined cohort (99.4%). Moderate overall agreement was found among Alt-AKI, KDIGO, and pRIFLE definitions ($\kappa = 0.18$, 95% *CI* 0.1–0.27) in which KDIGO and pRIFLE showed moderate agreement ($\kappa = 0.48$, 95% *CI* 0.36–0.60).

Conclusions Compared to pRIFLE and KDIGO criteria, Alt-AKI criteria detected more patients with cisplatin nephrotoxicity. pRIFLE is more sensitive to detect not only actual kidney injury but also patients at risk of cisplatin nephrotoxicity, while KDIGO seems more useful to detect clinically significant kidney injury.

Keywords Cisplatin · Nephrotoxicity · Kidney injury · Electrolyte · Children · Pediatrics

Introduction

Cisplatin is an antineoplastic agent that is effective and widely used for treating childhood malignancies: it is a standard component of chemotherapy in many pediatric malignancies including neuroblastomas, sarcomas, and head and neck, brain, testicular, gynecologic, and hepatobiliary cancers [1]. Since the 1960s, the survival rate of pediatric cancer has increased from around 10 to nearly 80% today [2]. Unfortunately, cisplatin also exerts many important adverse effects that hamper its potential benefit [3–5].

One of cisplatin's notable adverse effects is nephrotoxicity, both acute and long-term [6, 7]. Cisplatin-induced nephrotoxicity mainly manifests as kidney tubular injury leading to electrolyte disturbances manifested as hypomagnesemia, hypokalemia, and hypophosphatemia and/or increased serum creatinine (occurring more than 7 days after treatment initiation) and decreased glomerular filtration rate [8, 9]. Hypomagnesemia is highly

A.H. Maitland-van der Zee and B.C. Carleton contributed equally to this work.

✉ Bruce C. Carleton
bcarleton@popi.ubc.ca

Extended author information available on the last page of the article

associated with cisplatin nephrotoxicity with an incidence of approximately 40–90% [10]. Magnesium depletion may lead to hypokalemia and hypophosphatemia although renal potassium and phosphate wasting may occur as a result of platinum-mediated damage to tubular membranes [11]. In addition, cisplatin also has direct toxic effects on all glomerular components (i.e., glomerular capillaries, basement membrane, epithelial podocytes, mesangial cells, and parietal cells of Bowman's capsule) manifested in histological abnormalities affecting all these structures [12]. Depending on the outcome definition used, approximately 60–80% and 10–30% of children and adolescents treated with cisplatin are reported to experience chronic glomerular and tubular nephrotoxicity, respectively [8]. In addition, the risk of developing kidney failure in childhood cancer survivors is nine-fold higher compared with their siblings [8]. Platinum agents can be detected 20 years after use, raising concerns of long-term toxicity in pediatric cancer survivors [13].

A systematic review reported that the prevalence of adverse kidney effects in general childhood cancer patients ranged from 0 to 84% [14]. Differences in defining nephrotoxicity among studies have contributed to variations in the incidence of nephrotoxicity beyond heterogeneity in clinical characteristics (e.g., different cancer and medications) and methodology (e.g., different follow-up period) [14]. Even when the same outcome measures were used, differences in defined cutoff for abnormal values were still observed among individual studies [14]. Most cisplatin nephrotoxicity studies have used creatinine-based measurements of kidney function. However, several studies have also included electrolyte abnormalities in order to capture cisplatin-induced kidney tubular injury. Creatinine-based kidney function and electrolyte abnormality can be studied both separately [15, 16] or as one combined definition [17, 18]. Selection of an appropriate definition of nephrotoxicity is important to identify both modifiable and non-modifiable risk factors for cisplatin-induced nephrotoxicity. Furthermore, risk factors could guide clinicians in targeting cisplatin-based chemotherapy to the right patients with a goal to reduce the risk of nephrotoxicity without compromising the effectiveness of therapy.

To date, no studies have ever compared the incidence of kidney injury using various accepted definitions such as the "Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease" (RIFLE) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications in pediatric oncology settings. The objectives of this study were to evaluate the incidence of kidney injury in two different cohorts of pediatric patients treated with cisplatin (Vancouver and Mexico City cohorts) and to compare the commonly used and alternative definitions for kidney injury.

Methods

Subjects

The Vancouver cohort consisted of pediatric patients (< 18 years) treated with cisplatin-based chemotherapy at the BC Children's Hospital, Vancouver, Canada. Initiation of cisplatin-based treatment took place between December 1988 and March 2011. Patients participated in the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) [19, 20].

The Mexico City cohort consisted of pediatric patients (< 18 years) treated with cisplatin-based chemotherapy at the Hospital Infantil de México Federico Gómez (HIMFG) or the Hospital de Pediatría Dr. Silvestre Frenk Freud (HPSFF) in Mexico City, Mexico. Initiation of cisplatin-based treatment took place between June 2002 and May 2013.

The study was approved by the research ethics boards of University of British Columbia and HIMFG and HPSFF. Written informed consent or assent was obtained from all patients or from the parents or legal guardians in the case of minors in compliance with the Helsinki Declaration.

Data collection

Information concerning clinical and demographic characteristics, chemotherapy-related data, concomitant medication, serum magnesium levels (Mg), serum potassium levels (K), serum phosphate levels (PO_4), serum creatinine (SCr) levels, and glomerular filtration rate (GFR) was extracted from the medical records. Estimated GFR was calculated if no GFR was available in the medical records by using Bedside-Schwartz formula [21].

Outcome definition

KDIGO definition

Nephrotoxicity was defined by using SCr criteria of the KDIGO acute kidney injury (AKI) definition [22]. Nephrotoxicity was defined as ≥ grade 1 AKI (≥ 50% rise or ≥ 26.5 µmol/L rise in SCr from baseline) (Table 1). Urine output criteria were not included since cisplatin-induced nephrotoxicity is nonoliguric [16]. Forty-eight hours or 7 days timing criteria were not used because (1) these criteria are intended for ICU patients [16, 22], (2) increases of SCr due to cisplatin therapy may occur beyond 7 days after treatment started [9], and (3) cisplatin was intended to be given in a repeated manner.

Table 1 Nephrotoxicity definitions used in this study

KDIGO	≥ grade 1 AKI (≥ 50% rise or ≥ 26.5 µmol/L rise in SCr from baseline)
pRIFLE	≥ 25% fall in GFR from baseline
Alt-AKI	Grade 1: asymptomatic electrolyte disorders (hypomagnesemia, hypokalemia, or hypophosphatemia), including an increase in SCr, up to 1.5 times baseline value Grade 2: Need for electrolyte supplementation for less than 3 months and/or increase in SCr 1.5–1.9 times from baseline Grade 3: increase in SCr 2–2.9 times from baseline or need for electrolyte supplementation for more than 3 months after treatment completion Grade 4: increase in SCr ≥ 3 times from baseline or kidney replacement therapy

pRIFLE definition

GFR reduction was categorized as per pRIFLE criteria. AKI was defined as ≥ grade "Risk" or ≥ grade 1 AKI (≥ 25% fall in GFR from baseline) (Table 1) [23]. GFR values from the database were used. The estimated GFR was used if there was no GFR available in the medical reports. Urine output criteria were not included since cisplatin-induced nephrotoxicity is nonoliguric [16].

Electrolyte abnormalities (hypokalemia, hypophosphatemia, and hypomagnesemia)

Electrolyte abnormalities were defined as ≥ grade 1 hypokalemia, hypophosphatemia, and hypomagnesemia (< lower limit of normal (LLN)) for age, using the laboratory reference ranges as mentioned in the Common Terminology Criteria for Adverse Events (CTCAE) v.5 [24].

Alternative definition (Alt-AKI)

The alternative definition combined SCr and electrolyte supplementation status to assess kidney function acutely, as previously described [17]. Patients who developed cisplatin-induced nephrotoxicity were classified as cases (grade 1–4), while those who did not develop cisplatin-induced nephrotoxicity were defined as controls (grade 0) (Table 1).

The grading of nephrotoxicity was as follows: grade 0 – normal kidney function; grade 1 – asymptomatic electrolyte disorders (hypomagnesemia, hypokalemia, or hypophosphatemia), including an increase in SCr, up to 1.5 times baseline value; grade 2 – need for electrolyte supplementation (magnesium, potassium, or phosphate) for less than 3 months after treatment completion and/or increase in SCr 1.5–1.9 times from baseline; grade 3 – increase in SCr 2–2.9 times from baseline or need for electrolyte supplementation (magnesium, potassium, or phosphate) for more than 3 months after treatment completion; and grade 4 – increase in SCr ≥ 3 times from baseline or kidney replacement therapy [17]. The decision to initiate electrolyte supplementation was made by the treating oncologist according to local clinical guidelines or practice patterns.

The outcome definitions above were analyzed at the following time points:

1. Baseline: the lowest SCr value or the lowest electrolyte value (magnesium, phosphate, potassium, sodium) within the 3-month period before the start date of cisplatin therapy. If no baseline SCr was available, a normal estimated GFR 120 mL/min/1.73 m^2 was assumed, and SCr was back-calculated from the Bedside-Schwartz formula. Prior to cisplatin chemotherapy, electrolyte values can easily fluctuate due to various non-renal factors (e.g., diet, hydration). We selected the lowest (worst) value of electrolyte baseline because we do not want to overestimate the incidence of electrolyte imbalances.
2. During cisplatin therapy: for the Vancouver cohort, the highest SCr or lowest electrolyte value (magnesium, phosphate, potassium, sodium) between the first day and 90 days after the last cisplatin administration was used. For the Mexico City cohort, a minimum follow-up period of 1 year since the initiation of cisplatin was used.

Statistical analysis

Data were analyzed by using IBM SPSS v.26 (IBM Corp, NY, USA). Descriptive statistics were used to assess differences between pediatric patients with and without cisplatin-induced toxicities. Median and interquartile range (IQR) were computed for continuous variables instead of means and standard deviations (SD) if the data were not normally distributed. Fisher's exact test and Mann–Whitney *U* test were used to examine differences in the distribution of categorical and continuous variables, respectively. Definitional overlap between KDIGO, pRIFLE, and Alt-AKI were reported as actual value and percentage. Inter-definition reliability was calculated using Cohen's and Fleiss' kappa method for two and more than two outcome definitions, respectively. The kappa value was interpreted based on

Landis and Koch [25]. All statistical tests were 2-sided and a threshold of $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

Data were available for 100 and 73 cisplatin-treated patients from Vancouver and Mexico City, respectively (Table 2). Sex composition and age at start of treatment were comparable between both cohorts. The Vancouver cohort had more diverse cancer types. The most commonly diagnosed cancers within the Vancouver cohort were osteosarcoma (25%) while in the Mexico City cohort, the most common cancers were germ cell tumors (31.5%). The cisplatin cumulative dose was significantly higher in the Mexico City cohort (median: 524 vs. 400 mg/m^2). Aminoglycosides, furosemide, and vancomycin were the three most commonly concomitantly administered potentially nephrotoxic medications in the Vancouver cohort (49%, 45%, and 37%, respectively). Meanwhile, aminoglycosides, vancomycin, and ifosfamide were the three most commonly concomitantly administered potentially nephrotoxic medications in the Mexico City cohort (34.2%, 13.6%, and 10.9%, respectively). The percentage of patients receiving radiation was significantly higher in the Vancouver cohort (40% vs. 9.5% in the Mexico City cohort) with 10% of the Vancouver patients receiving abdominal radiation. Electrolyte supplementation was administered during chemotherapy to 77% of patients in the Vancouver cohort. However, no data on electrolyte supplementation during on-treatment period was available from the Mexico City cohort. Although baseline SCr between both cohorts was similar, GFR baseline was significantly lower in the Mexico City cohort compared to the Vancouver cohort (median: 150 vs. 125 mL/min/1.73 m^2).

Incidence of nephrotoxicity

The incidences of nephrotoxicity based on different outcome definitions in both cohorts are available in Table 3. Overall, nephrotoxicity was consistently more common in the Vancouver versus Mexico cohort, based on both SCr definitions and electrolyte abnormalities. However, the differences were

Table 2 Baseline characteristics of the study population in both datasets

Characteristics	Vancouver cohort ($n = 100$)	Mexico City cohort ($n = 73$)	*P*-value
Time of inclusion, range, months	267	132	
Sex, male, no. (%)	58 (58.0)	40 (54.8)	0.756
Age at start treatment, median (IQR), years	5.9 (2.2–11.8)	7.5 (3.0–13.4)	0.295
Type of cancer, no (%)			
Germ cell tumor	15 (15.0)	23 (31.5)	< 0.001*
Hepatoblastoma	8 (8.0)	18 (24.7)	
Medulloblastoma	14 (14.0)	0 (0)	
Neuroblastoma	23 (23.0)	5 (6.8)	
Osteosarcoma	25 (25.0)	15 (20.5)	
Other	15 (15.0)	12 (16.4)	
Cisplatin cumulative dose, median (IQR), mg/m^2	400 (265–460)	524 (415–718)	< 0.001*
Concomitant nephrotoxic medication, no. (%)			
Aminoglycosides	49 (49.0)	25 (34.2)	0.06
Acyclovir	26 (26.0)	2 (2.7)	< 0.001*
Amphotericin	27 (27.0)	0 (0)	< 0.001*
Ifosfamide	22 (22.0)	8 (10.9)	0.07
Methotrexate	29 (29.0)	1 (1.4)	< 0.001*
Furosemide	45 (45.0)	0 (0)	< 0.001*
Vancomycin	37 (37.0)	10 (13.6)	< 0.001*
Radiation total, no. (%)	40 (40.0)	7 (9.5)	< 0.001*
Abdominal radiation, no (%)	10 (10.0)	NA	NA
Electrolyte supplementation during chemotherapy, no. (%)	77 (77.0)	NA	NA
Baseline (SCr), median (IQR), µmol/L	33 (22–43)	34 (27–40)	0.890
Baseline (GFR), median (IQR), mL/min/1.73 m^2	150 (120–190)	125 (106–167)	0.001*

NA, not available/not recorded. *$P < 0.05$ based on Fisher's exact test (for nominal outcome variable) and Mann–Whitney *U* test (for continuous outcome variable)

Table 3 Nephrotoxicity based on different outcomes in Vancouver and Mexico city cohort

Outcome	Nephrotoxicity[a] no. (%)						*P*-value
	Vancouver cohort ($n=100$)			Mexico City cohort ($n=73$)			
	Yes	No	NA[b]	Yes	No	NA[b]	
KDIGO	49 (50.0)	49 (50.0)	2	28 (38.4)	45 (61.6)	0	0.162
pRIFLE	78 (81.3)	18 (18.8)	4	32 (43.8)	41 (56.2)	0	< 0.001*
Electrolyte disturbance							
Hypokalemia	47 (48.0)	51 (52.0)	2	6 (9.1)	60 (90.9)	7	< 0.001*
Hypophosphatemia	58 (60.4)	38 (39.6)	4	16 (24.2)	50 (75.8)	7	< 0.001*
Hypomagnesemia	88 (88.9)	11 (11.1)	1	7 (10.6)	59 (89.4)	7	< 0.001*
Alt-AKI	90 (91.8)	8 (8.2)	2	53 (72.6)	20 (27.4)	0	0.001*

[a]Toxicity was defined as ≥ grade 1. [b]Undetermined due to data inavailability. *$P<0.05$ based on Fisher's exact test

not statistically significant by the KDIGO definition. The pRIFLE definition resulted in more nephrotoxicity cases than the KDIGO definition both in the Vancouver cohort (81.3% vs. 50%) and in the Mexico City cohort (43.8% vs. 38.4%). In the Vancouver cohort, hypomagnesemia was the most common electrolyte abnormality (88.9%) while hypophosphatemia was the most common electrolyte abnormality in the Mexico City cohort (24.2%). The use of the Alt-AKI resulted in higher nephrotoxicity (91.8% in the Vancouver and 72.6% in the Mexico City cohorts) compared to the SCr-based definition in both cohorts.

To examine the potential impact of the number of different nephrotoxic medications and their durations of use, data on aminoglycoside (gentamicin, amikacin, and tobramycin) used concomitantly with cisplatin therapy was examined in the Vancouver cohort ($n=49$) followed by the data on furosemide and vancomycin usage. The number of concomitant nephrotoxic medications per patient was significantly higher in patients with nephrotoxicity compared to patients without nephrotoxicity (median: 3 vs. 1 drugs) when pRIFLE criteria were applied. Meanwhile, duration of vancomycin administration was longer in patients with nephrotoxicity compared to patients without nephrotoxicity when Alt-AKI definition was used (median: 8 vs. 4 days) (Table S1).

The severity of nephrotoxicity was further analyzed (Fig. 1). In KDIGO and pRIFLE outcomes, the higher the severity of nephrotoxicity, the smaller the number of patients. However, a similar pattern was not observed when the Alt-AKI definition was applied. In both cohorts, most of the nephrotoxicity was classified as grade 1 for KDIGO definition (31.6% in the Vancouver cohort; 26% in the Mexico City cohort) and as "Risk" for pRIFLE definition (37.5% in Vancouver cohort; 32.9% in Mexico City cohort). The largest differences of nephrotoxicity incidence were found in the lowest grade of nephrotoxicity (grade 1 nephrotoxicity of KDIGO and "Risk" criteria of pRIFLE definition). When applying pRIFLE criteria, the incidence was increased from 31.6 to 37.5% in Vancouver cohort and from 26 to 32.9% in Mexico City cohort. Based on Alt-AKI, most nephrotoxicity cases were categorized as grade 2 in the Vancouver cohort (61.2%) and grade 3 in the Mexico City cohort (34.2%). Overall, based on KDIGO, pRIFLE, and Alt-AKI, the decline of kidney function is more significant in the Vancouver cohort than in the Mexico City cohort.

Most cases of electrolyte abnormality manifested as mild (grade 1) and mild-to-moderate toxicity (grade 2) (Fig. 2). The severity of electrolyte abnormalities in the Mexico City cohort could not be further explored due to data

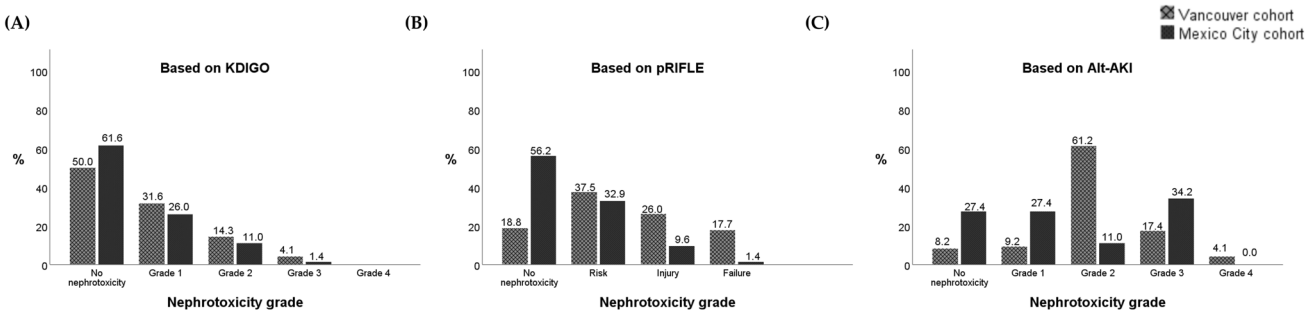

Fig. 1 Comparison of nephrotoxicity between Vancouver and Mexico City cohort in different outcome definitions. **A** Based on KDIGO, **B** based on pRIFLE, **C** based on Alt-AKI definition

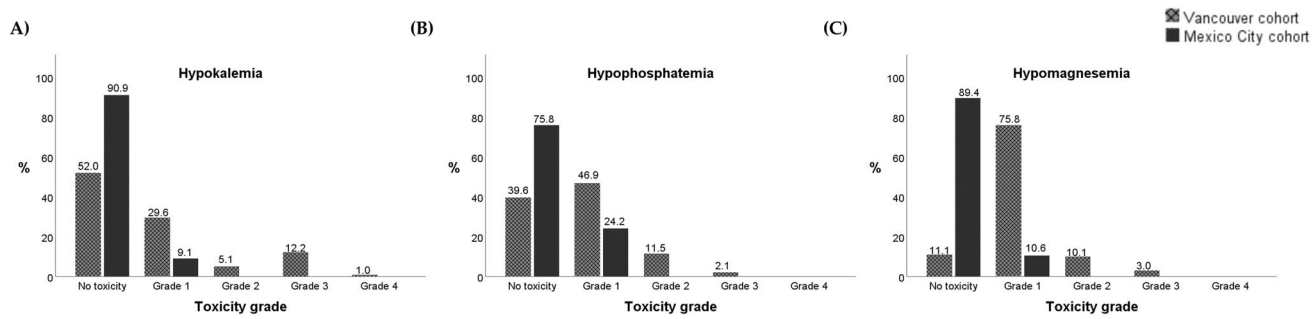

Fig. 2 Comparison of electrolyte abnormalities between Vancouver and Mexico City cohort. **A** Hypokalemia, **B** hypophosphatemia, **C** hypomagnesemia

unavailability. In general, electrolyte abnormalities were more common in the Vancouver cohort with hypomagnesemia showing the most significant difference in incidence compared to the Mexico City cohort (88.9% vs. 10.6%). In the Vancouver cohort, the percentage of moderate-to-severe and severe electrolyte disturbance (≥ grade 2) was higher in hypokalemia compared to hypophosphatemia and hypomagnesemia (18.3% vs. 13.6% vs. 13.1%).

Definitional overlap

The definitional overlap among standardized nephrotoxicity definition is shown in Fig. 3. The Vancouver cohort had higher overlap between definitions compared to the Mexico City cohort (44.7% vs. 27.4%). Overall, overlap among the three definitions in the combined dataset was 37.1%. The KDIGO definition consistently provided the highest overlap with at least one other nephrotoxicity definition within the Vancouver cohort (100%), Mexico City cohort (98.6%), and combined cohorts (99.4%). Alt-AKI showed the lowest overlap with at least one nephrotoxicity definition within the Vancouver (86.2%), Mexico City (60.3%), and combined cohorts (74.8%).

Interdefinition reliability

The reliability of definition pairs was tested in each cohort and the combined cohort (Table 4). In the Vancouver cohort, fair agreement was found between the KDIGO and pRIFLE definitions ($\kappa = 0.21$, 95% *CI* 0.06–0.37) while poor agreement was found between Alt-AKI and KDIGO definitions ($\kappa = -0.13$, 95% *CI* −0.24, −0.02). In the Mexico City cohort, substantial agreement between the KDIGO and pRIFLE definitions was observed ($\kappa = 0.77$, 95% *CI* 0.63–0.92). In the combined cohort, significantly moderate agreement between the KDIGO and pRIFLE definitions was identified ($\kappa = 0.48$, 95% *CI* 0.36–0.60). Overall, a moderate agreement was found among three nephrotoxicity definitions by applying Fleiss' kappa method ($\kappa = 0.18$, 95% *CI* 0.1–0.27).

Discussion

Main findings

Our study demonstrated that nephrotoxicity is common among children treated with cisplatin. Depending on the definition used, cisplatin-induced nephrotoxicity occurred in 38–92% of the children. The KDIGO criteria provided the highest overlap in cases with other definitions in both cohorts. A moderate agreement was found among three nephrotoxicity definitions in the combined cohort.

The Alt-AKI definition resulted in the highest nephrotoxicity incidence and severity compared to KDIGO and pRIFLE since asymptomatic electrolyte disorders even without increases of SCr were included as nephrotoxicity (Alt-AKI grade 1) and most cisplatin-treated patients receive electrolyte supplementation (Alt-AKI grade 2). Compared to pRIFLE, KDIGO showed fewer patients with nephrotoxicity during cisplatin therapy which confirms previous research conducted in hospitalized children [26] and children who received liver transplantation [27]. The definition based on SCr abnormalities is expected to reveal fewer cases than a definition based on GFR because an actual substantial fall in GFR is present before the SCr becomes abnormal [28].

The largest differences of nephrotoxicity incidence were found in the lowest grade of nephrotoxicity (grade 1 nephrotoxicity of KDIGO and "Risk" criteria of pRIFLE definition). The incidence of nephrotoxicity becomes higher when pRIFLE criteria were applied. This is due to the fact that pRIFLE criteria defined subjects in the risk category (grade "Risk" with GFR reduction from 0 to 25% from baseline) as subjects with kidney injury. In contrast, grade 1 kidney injury of KDIGO applied when the SCr rose to more than 1.5 times the baseline value and did not apply when SCr only rose to a value between 1 and 1.5 times the baseline value. Therefore, KDIGO is likely more useful to detect clinically significant kidney injury while pRIFLE is more sensitive to detect not only the actual kidney injury but also the patients who are at risk for developing kidney injury.

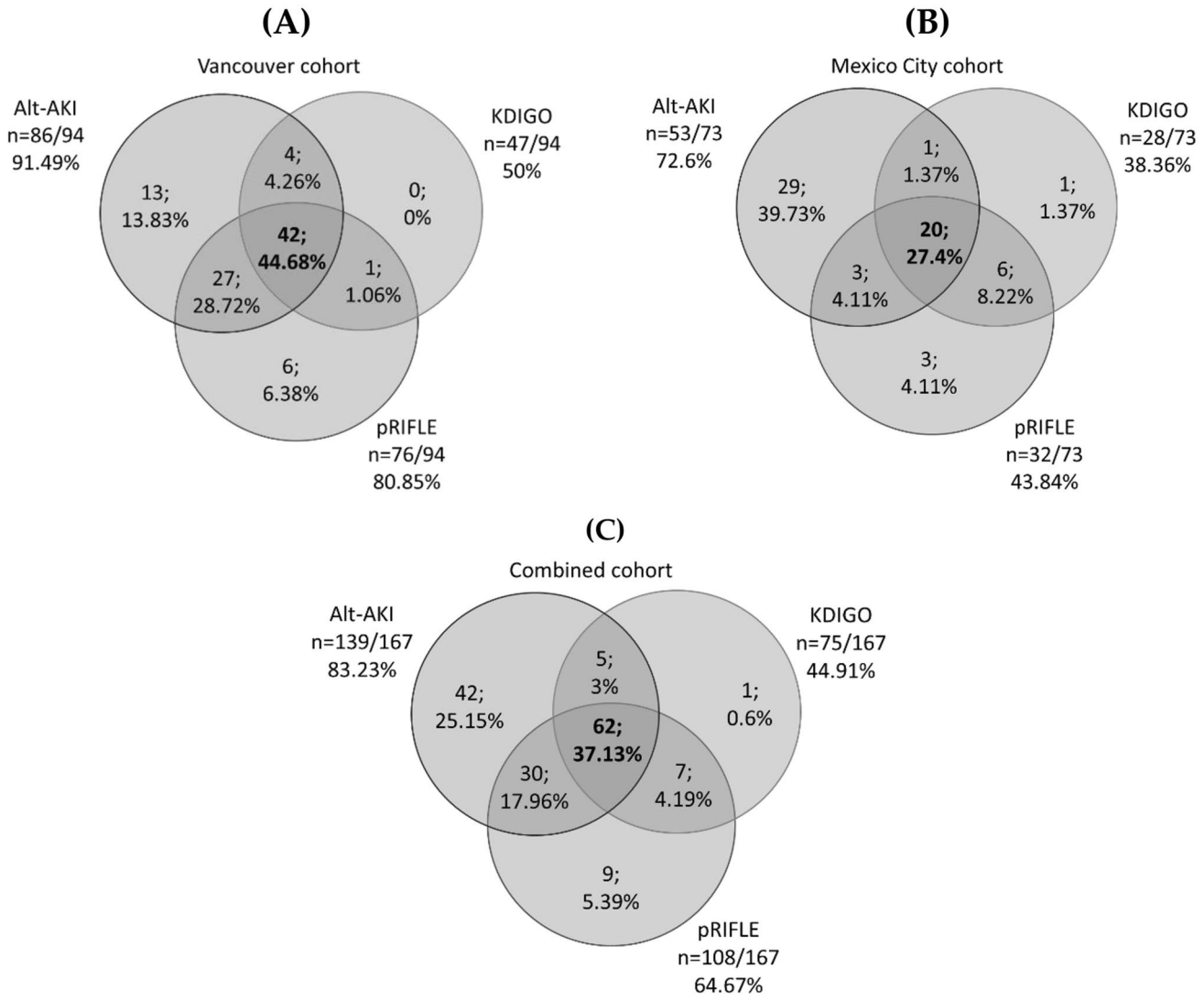

Fig. 3 Overlap in the nephrotoxicity definitions during cisplatin chemotherapy in Vancouver cohort (**A**), Mexico City cohort (**B**), and combined cohort (**C**)

Table 4 The reliability between two outcome definitions in Vancouver, Mexico City, and combined cohort

Cohort	Tested outcome definitions	κ (95% *CI*)	Agreement interpretation	*P*-value
Vancouver	KDIGO–pRIFLE	0.21 (0.06–0.37)	Fair	0.009*
	KDIGO–Alt-AKI	−0.13 (−0.24–−0.02)	Poor	0.027*
	pRIFLE–Alt-AKI	−0.05 (−0.20–0.11)	Poor	0.617
Mexico City	KDIGO–pRIFLE	0.77 (0.63–0.92)	Substantial	< 0.001*
	KDIGO–Alt-AKI	0.03 (−0.15–0.21)	Slight	0.717
	pRIFLE–Alt-AKI	−0.01 (−0.20–0.18)	Poor	0.902
Combined	KDIGO–pRIFLE	0.48 (0.36–0.60)	Moderate	< 0.001*
	KDIGO–Alt-AKI	0.10 (0.00–0.21)	Slight	0.057
	pRIFLE–Alt-AKI	0.06 (−0.08–0.20)	Slight	0.361

*$P < 0.05$ using Cohen's kappa method

Variability in the incidence of nephrotoxicity occurred not only across different definitions but also across different cohorts. In the Vancouver cohort, there was a higher number of cases of nephrotoxicity and electrolyte abnormalities than in the Mexico City cohort despite lower cisplatin cumulative dose and higher baseline GFR. This difference is most likely due to more concomitant nephrotoxic medication administered in the Vancouver cohort. As an example, the high proportion of patients receiving furosemide and amphotericin potentially led to higher hypokalemia incidence in the Vancouver cohort compared to the Mexico City cohort.

The lower cumulative dose observed in the Vancouver cohort probably was a result of different regimens chosen both within the same cancer and across different cancers. The Mexico City cohort has a higher rate of germ cell tumors, which was linked to the administration of daily low dose of cisplatin over 5 days (20 mg/m^2 per day or 100 mg/m^2 per cycle). As a result, the Mexico City cohort has high cisplatin cumulative dose but very low daily dose which may explain why fewer nephrotoxicity cases occurred in the Mexico City cohort. This intensity-dependent cisplatin toxicity is also reported in previous studies, both for nephrotoxicity and ototoxicity [29, 30]. Other clinical factors including shorter administration time, concurrent treatment with other nephrotoxins (e.g., ifosfamide/loop diuretics/aminoglycosides), increased peak serum or urine platinum concentrations (interindividual differences in pharmacokinetics), and older age are reported to increase the risk of cisplatin-induced kidney injury in children [6, 7].

Considering differences in ancestry between the two cohorts, variation in pharmacogenetic variants might also explain the outcome variabilities in this study. Previous studies suggest that variation in genes involved in cisplatin pharmacodynamics and pharmacokinetics may contribute to cisplatin nephrotoxicity [5, 31–38]. A variant in *SLC22A2*, a gene that encodes an important cisplatin transporter in kidney tubular cells (organic cation transporter 2; OCT2), is an example [39]. Based on the Allele Frequency Aggregator (ALFA) database, the minor allele frequency (MAF) of a risk variant for cisplatin nephrotoxicity, rs316019, is almost twice as high in the European population compared to Latin American, including Mexican (10% vs. 5.6%) [40]. This may also explain why children in the Vancouver cohort experienced more nephrotoxicity.

Even though it is widely used in clinical settings, SCr is not an ideal biomarker for drug-induced kidney injury. SCr is influenced by renal and non-renal factors independent of kidney function [41]. For example, low muscle mass is common in children with cancer [3]. Rises in SCr among cisplatin-treated patients can also occur beyond 7 days reflecting a subacute instead of acute injury [9]. In addition, creatinine—to a small extent—competes with cisplatin for excretion as both are substrates for OCT2 [42]. eGFR that is used in this study is less accurate in the non-steady state (i.e., acute kidney injury). Moreover, several factors affecting the production of creatinine are not included in the eGFR formulae (i.e., level of exercise, diet, neuromuscular diseases leading to loss of muscle mass, and disease states affecting the rate of conversion of creatine to creatinine) [43]. Thus, it is important to include other clinical characteristics of cisplatin-associated kidney injury alongside the established creatinine-based definitions as a starting point. Electrolyte losses were evident characteristics of cisplatin-induced tubular dysfunction due to kidney tubular injury [11]. Despite supplementation, the incidence of hypomagnesemia was arguably high in this study, especially in the Vancouver cohort. A previous study reported that magnesium deficiency may enhance acute kidney injury through amplification of kidney platinum accumulation [44]. This could also explain why we found a higher nephrotoxicity incidence in Vancouver cohort than in Mexico City cohort.

Due to the unique characteristics of cisplatin nephrotoxicity, a reliable definition is clearly needed to accurately capture the significance of cisplatin nephrotoxicity and determination of risk factors to further assist stratification of cisplatin therapy and needed interventions. The Alt-AKI definition was intended to incorporate both serum creatinine and electrolyte-based kidney injury to approximate the clinical characteristics of cisplatin nephrotoxicity. The rationale is that increased SCr often occurs in later stages and kidney injury usually manifests as electrolyte abnormalities due to tubular injury in cisplatin-treated children [9, 16]. However, the severity of nephrotoxicity is not distributed continuously as indicated by the small overlap with the creatinine-based definition.

Clinical relevance

In the absence of a single definition of cisplatin-induced nephrotoxicity, our findings indicate that KDIGO provides the most reliable definition to detect actual kidney injury during cisplatin-based chemotherapy in children. However, using pRIFLE might add more benefit when cisplatin-based chemotherapy is still considered to be administered to a patient with nephrotoxicity risk (e.g., patients with pre-existing kidney impairment or with borderline GFR value: 61–70 mL/min/1.73 m^2) as pRIFLE is more sensitive to capture the risk of kidney injury. Since nephrotoxicity is commonly found in cisplatin-treated children, electrolyte abnormalities can also help in understanding a patient's kidney function, especially in the early stage of cisplatin therapy. Incorporating electrolyte abnormalities to detect potential cisplatin-induced nephrotoxicity becomes more important due to the absence of a biomarker for cisplatin-specific nephrotoxicity or a specific definition.

Strengths and limitations

Our study compared multiple standardized kidney function definitions and an alternative definition to better characterize the incidence of cisplatin-induced nephrotoxicity. Furthermore, this study included two different cohorts from different populations to consider population heterogeneity and enhance the generalizability of the results. The study was also conducted in children, which reduces the effect of comorbidities affecting kidney function (e.g., pre-existing kidney injury, hypertension, heart failure, diabetes) on the results compared to adults. For example, pediatric patients tend to receive fewer concomitant and chronic nephrotoxic medications (e.g., NSAIDs) than adults and have lower rates of cardiovascular comorbidity which can affect the incidence of kidney impairment.

There were several limitations in our study. Since Mexican participant centers are third level care hospitals, the differences in cancer type between the two cohorts are most likely related to differences in referral patterns. The retrospective study design resulted in unavoidable information bias due to missing data on existing records. Several data elements were not available from the Mexico City cohort (e.g., ancestry, duration of cisplatin therapy, abdominal radiation status, electrolyte supplementation status, and selected concomitant nephrotoxic medications). Furthermore, in pediatric cancer, cisplatin was often administered in combination with other nephrotoxic antineoplastic agents such as ifosfamide and methotrexate. Therefore, distinguishing the effect of cisplatin from other nephrotoxic antineoplastic agents was a challenge. Differences in inclusion period between two cohorts could also have contributed to differences in treatment protocols (e.g., hydration) between the two centers. Differences in length of follow-up period could also contribute to the nephrotoxicity prevalence although we expected the most severe cisplatin nephrotoxicity occurs in the acute stage (< 90 days). Although different outcomes were used in this population, the disadvantages remain similar. For example, SCr is already widely used and regularly tested in patients; however, it can be influenced by various non-renal factors such as age, sex, diet, and concomitant drugs (e.g., cimetidine and trimethoprim). Moreover, SCr rises are late in the course of developing kidney impairment, resulting in failed early detection of nephrotoxicity [9]. Electrolyte disturbance is also highly influenced by hydration, diet, and other drugs, among other factors. In CTCAE-based electrolyte abnormalities, setting grade 2 as a cutoff value instead of grade 1 could increase its clinical significance.

Future research

A recently published article highlighted the importance of studying the impact of cisplatin-induced kidney injury on mortality [45]. For studies like that, the validity of definitions of cisplatin nephrotoxicity is critical. Moreover, future studies that define the cisplatin nephrotoxicity phenotype using sensitive and specific urinary biomarkers such as urinary kidney injury molecule-1 (KIM-1), β2-microglobulin (B2M), cystatin C, clusterin, and trefoil factor-3 (TFF-3) [41] would add more insights to cisplatin nephrotoxicity and its underlying mechanisms. Such studies will help clinicians in identifying patients with nonmodifiable risk factors for cisplatin-induced nephrotoxicity and how to deal with modifiable risk factors to prevent cisplatin-induced nephrotoxicity. The findings could further help risk stratification and personalize cisplatin therapy by guiding the selection and modification of therapy. This personalized approach is essential to avoid or treat such toxicity without compromising the effectiveness of chemotherapy.

The impact of cisplatin-induced nephrotoxicity and other long-term outcomes in children also warrants further investigations. Understanding the association between AKI and chronic kidney disease would be an important and relevant objective. Moreover, chemotherapy during childhood cancer has been associated with delayed growth [46]. Thus, bone health assessment among cisplatin-treated children (evaluated as longitudinal growth or height) and further follow-up among adults (measured as risk of osteoporosis and risk of fractures) would be valuable to understand the impact of chemotherapy in childhood cancer.

Conclusion

The incidence of cisplatin-induced nephrotoxicity in the Vancouver and Mexico City cohorts is high. Compared to pRIFLE and KDIGO criteria, Alt-AKI criteria detected more patients with cisplatin-induced nephrotoxicity. pRIFLE is more sensitive to detect not only the actual kidney injury but also the patients at risk while KDIGO is likely more useful to detect the clinically significant kidney injury. However, such creatinine-based definitions should be complemented with clinically significant electrolyte abnormalities, especially hypomagnesemia to capture the accurate clinical characteristics of cisplatin-induced nephrotoxicity. Establishment and validation on new cisplatin-induced nephrotoxicity are needed to help in mapping the incidence of cisplatin nephrotoxicity and to further guide a more risk-adapted cisplatin therapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-022-05632-z.

Acknowledgements We gratefully acknowledge the participation of all patients and families who took part in this study. We also acknowledge the contributions of the Canadian Pharmacogenomics Network for

Drug Safety (CPNDS) Consortium and Mexican Cooperative Oncology Network (MexiCON).

Author contribution Conceptualization: ZZ, SV, AHM, and BC; methodology: ZZ, SV, AHM, and BC; validation: ZZ and COH; formal analysis: ZZ and COH; investigation: ZZ and COH; resources: BC and MM; data curation: SRR, MM, RR, and BC; writing—original draft preparation: ZZ; writing—review and editing: ZZ, COH, SV, RM, SRR, MM, RR, AHM, and BC; visualization: ZZ; supervision: SV, RM, AHM, and BC; project administration: ZZ and COH; funding acquisition: ZZ, BC, and MM.

Funding This research was funded by Indonesia Endowment Fund for Education (LPDP) Ministry of Finance, the Republic of Indonesia (as a part of ZZ's Ph.D. project, grant no. 20161022049506). The APC was funded by Indonesia Endowment Fund for Education (LPDP). The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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Authors and Affiliations

Zulfan Zazuli[1,2] · Catharina J. P. Op 't Hoog[3] · Susanne J. H. Vijverberg[1] · Rosalinde Masereeuw[3] · Shahrad Rod Rassekh[4] · Mara Medeiros[5,6] · Rodolfo Rivas-Ruiz[7] · Anke H. Maitland-van der Zee[1] · Bruce C. Carleton[8,9,10]

1 Department of Respiratory Medicine, UMC Location University of Amsterdam, Amsterdam, The Netherlands

2 Department of Pharmacology-Clinical Pharmacy, School of Pharmacy, Bandung Institute of Technology, Bandung, Indonesia

3 Division of Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

4 British Columbia Children's Hospital, Division of Hematology/Oncology/Bone Marrow Transplantation, Department of Pediatrics, The University of British Columbia, Vancouver, BC, Canada

5 Hospital Infantil de México Federico Gómez, Ciudad de Mexico, México

6 Departamento de Farmacología, Facultad de Medicina, Universidad Nacional Autónoma de México, Ciudad de Mexico, México

7 Centro de Adiestramiento en Investigación Clínica, Coordinación de Investigación en Salud, Centro Médico Nacional Siglo XXI, IMSS, Mexico City, Mexico

8 BC Children's Hospital Research Institute, Vancouver, BC, Canada

9 Division of Translational Therapeutics, Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

10 Pharmaceutical Outcomes Program, British Columbia Children's Hospital, Vancouver, BC, Canada